Risk of thromboembolic events with endovascular cooling catheters in patients with subarachnoid hemorrhage

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Abstract: INTRODUCTION: Endovascular cooling is currently used for hypothermia treatment and fever reduction therapy. At the same time, little is known about the risks associated to endovascular cooling in patients treated with an endovascular cooling catheter (ECC). METHODS: A retrospective chart review of 122 patients with subarachnoid hemorrhage (SAH) treated with an ECC either for therapeutic hypothermia or for fever reduction was performed. ECC-associated thromboembolic events (TEE) such as pulmonary embolism and thrombosis were recorded and compared between patients treated with an ECC and patients treated only with a central venous line (CVL). Additionally, various laboratory parameters were recorded to determine if they might be related to the frequency of TEE's. RESULTS: 43 Patients were treated with an ECC and 79 with a CVL. Patients in the ECC group suffered more frequently from TEE (37 %) than those with a CVL (5 %). None of the laboratory parameters was associated with an increased TEE risk. The treatment with an ECC alone was a risk factor for a TEE, independent from age as well as from Hunt and Hess grade. CONCLUSION: Our data show that the treatment with ECC increases the risk of TEE in SAH patients. Therefore, especially when considered for fever reduction, non-invasive devices for surface cooling should be the first choice.

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Risk of Thromboembolic Events with Endovascular Cooling Catheters in Patients with Subarachnoid Hemorrhage

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Abstract:

Introduction: Endovascular cooling is currently used for hypothermia treatment and fever reduction therapy. At the same time, little is known about the risks associated to endovascular cooling in patients treated with an endovascular cooling catheter (ECC).

Methods: A retrospective chart review of 122 patients with subarachnoid haemorrhage (SAH) treated with an ECC either for therapeutic hypothermia or for fever reduction was performed. ECC associated thromboembolic events (TEE) such as pulmonary embolism and thrombosis were recorded and compared between patients treated with an ECC and patients treated only with a central venous line (CVL). Additionally, various laboratory parameters were recorded to determine if they might be related to the frequency of TEE´s.

Results: 43 Patients were treated with an ECC and 79 with a CVL. Patients in the ECC group suffered more frequently from TEE (37%) than those with a CVL (5%). None of the laboratory parameters was associated with an increased TEE risk. The treatment with an ECC alone was a risk factor for a TEE, independent from age as well as from Hunt and Hess grade.

Conclusion: Our data show that the treatment with ECC increases the risk of TEE in SAH patients. Therefore, especially when considered for fever reduction, non-invasive devices for surface cooling should be the first choice.

Keywords:

Therapeutic hypothermia, subarachnoid haemorrhage, stroke, endovascular cooling, endovascular cooling catheter, thromboembolic event, thrombosis, pulmonary embolism

Introduction:

Therapeutic hypothermia has neuroprotective effects in adults after cardiopulmonary resuscitation [1]. Fever has been identified as a risk factor for poor outcome in patients with ischemic stroke [2] subarachnoid hemorrhage (SAH) [3], intracerebral hemorrhage [4] or traumatic brain injury [5].

For targeted, long-term temperature control, endovascularly based systems might have several advantages concerning efficacy and usability compared to surface cooling [6, 7]. The need for a central venous line, however, calls for an adequate risk assessment and evaluation of potential complications such as thromboembolic events (TEE), as these might be promoted by the long-term application of the device. Up to date, only small case series of patients with traumatic brain injury are described concerning this specific complication [8]. The aim of the present study was to analyze the incidence of TEE in a large cohort of patients with aneurysmal subarachnoid hemorrhage (SAH) treated with endovascular cooling catheters (ECC) compared to SAH patients treated with conventional central venous lines (CVL) and to identify potential risk factors.

Methods:

The study was approved by the ethics committee of the University Hospital of Zurich. A retrospective chart review was performed including all patients with aneurysmal SAH admitted to the Neurosurgical Intensive Care Unit of the University Hospital Zurich between January 2011 and March 2013 and treated with ECC for fever reduction or therapeutic hypothermia. Patients with a severe concomitant disease were excluded from the analysis. Indications for hypothermia treatment were brain edema with intracranial hypertension and/or symptomatic cerebral vasospasm refractory to conventional treatment. The correspondent treatment algorithms are previously described [9]. The following parameters were analysed: patient’s clinical state at admission by means of Hunt and Hess scale, type of catheter (CVL or ECC), date of catheter insertion and removal. Deep venous thrombosis (DVT) was evaluated by sonography if the patient showed any clinical signs of swelling, pain, elevated skin temperature or red/livid colour of the skin at the extremity in which the catheter was inserted or by screening in patients with suspected high risk for TEE. Pulmonary embolism was diagnosed with contrast-enhanced CT scan if the patient showed any symptoms or incidentally. The following daily measured parameters were analysed in the ECC group: fibrinogen, C reactive protein (CRP), procalcitonin C (PTC), leucocyte and thrombocyte counts. Vena cava filter were inserted because of DVT and coexistent strict contraindication for anticoagulation.

ECCs were changed routinely every 5 days or earlier if signs of infection occurred. CVLs were changed only with clinical signs of infection. Every patient’s individual, continuous ECC application period, from start until end of the treatment period (application from only one up to several catheters), was combined to one consecutive treatment event. If the continuous ECC treatment was interrupted for any reason, the patient was excluded from the study. The day of TEE diagnosis after ECC onset was recorded (provided the patient was still hospitalized in our department) irrespectively of whether the TEE occurred during the ECC application period or afterwards. If a patient suffered from more than one TEE, only the first one was considered the index event. From all TEE the median day of occurrence was calculated. This determined median day was applied to compare the above cited laboratory parameters in the ECC patients with TEE to those in patients without TEE. In both groups the laboratory parameters collected from the median day and the 4 preceding days were averaged. Prophylaxis against TEE was routinely performed with pneumatic stockings in combination with unfractionated heparin 5000 E/24h cont. i.v. started 6 hours after aneurysm clipping or aneurysm coiling.

The endovascular cooling system applied was a dual infusion lumen 8.5F 20-cm catheter (Cool Line Catheter, Zoll Medical, California, USA). This catheter is furnished with an additional lumen, which ends in two balloons (sized 55 mm in length and 5×5 mm in diameter). The balloons are perfused with a sterile Ringer's lactate solution via a closed-loop tubing system. The tubing system is connected to a temperature-management device (Coolgard System, Zoll Medical, California, USA), consisting of a temperature adjustable water bath (0.5 °C–42 °C) depending on the patient's own temperature [9]. Conventional CVL with 4- or 5- lumen (Arrow International Inc., Teleflex, Durham, NC, USA) were applied in all patients.

Statistical analysis: Patient characteristics, as well as fibrinogen, leucocyte, thrombocyte count, CRP, PCT values and severity (Hunt and Hess grade) were compared using Mann-Whitney-U test. Binominal variables were compared between the groups by the chi-square test or Fisher's exact test where appropriate. A value of $p<0.05$ was regarded as statistically significant. Bivariate logistic regressions were used to test the predictive power of treatment with ECC for development of TEE independently of age and Hunt and Hess grade. Calibration of the models was assessed using the Hosmer-Lemeshow test. Odds ratios (OR) were reported with 95% confidence intervals (CI). Full multiple logistic regressions were not performed because of the small number of events. IBM SPSS Statistics 21.0, Armonk, NY was used.

Results

A total of 122 patients with (SAH) was analyzed. 117 patients suffered from aneurysmal, 5 from non-aneurysmal SAH. Mean age of the patient population was 57.1 ± 12.2 years, severity grade according to Hunt and Hess was in mean 2.9 ± 1.3. Endovascular cooling catheters (ECC) were applied in 43 patients, either for fever treatment (22 patients) or therapeutic hypothermia (21 patients). During the same time period, 79 patients were not treated with ECCs and used as control group. In these patients only CVL were routinely applied. All ECCs were inserted into the femoral vein, whereas CVLs were inserted either in the subclavian (69 cases) or jugular vein (10 cases). Patients in the ECC group (53.1 ± 9.7 years) were younger than those in the CVL group (59.3 ± 12.9, $p = 0.004$). With 3.6 ± 1.2 the Hunt and Hess grade in the ECC group was higher than in the CVL group with 2.5 ± 1.2 ($p < 0.001$). Overall 20 patients (16%) died. Among them, 12 patients died under withdrawal of treatment due to brain herniation and/or multiple infarctions, 7 patients died with the signs of multiorgan failure due to sepsis syndrome and 1 because of a rebleeding. Mortality in patients with ECC was higher (14 among 43; 33%) compared to those with CVL (6 among 79; 8%; $p < 0.001$). There was no significant difference in mortality between patients treated for fever (6 among 21; 29%) compared to those treated with hypothermia (9 among 22; 41%).

Patients in the ECC group suffered more frequently from TEE (37%) than those with CVL (5%) ($p < 0.001$) (table 1). Thrombosis, confirmed by sonography, occurred more frequently in the ECC group (26%) compared to the CVL group (5%) ($p < 0.001$). Thrombosis occurred significantly more frequently in patients treated for fever (52%) than in patients treated with hypothermia (23%) ($p = 0.044$). Pulmonary embolism, confirmed with contrast-enhanced CT scan, occurred in 5 patients of the ECC group and in 2 patients of the CVL group ($p = 0.039$). Pulmonary embolism tended to occur more frequently in patients treated for fever, although without statistical significance. Because of strict contraindication for anticoagulation, 6 patients, all in the ECC group treated for fever were protected against pulmonary embolism with cava filters inserted into the inferior caval vein. All of them were on prophylaxis with heparin.

The treatment with ECC alone was a risk factor for TEE independent from age (OR 12.5, 95% CI 3.6 – 43.5); $p < 0.001$) as well as from Hunt and Hess grade (OR 8.9, 95% CI 2.5 - 31.25; $p = 0.001$).

The median day for the occurrence of TEE was day 15. In 32 patients of the ECC group, median values for fibrinogen, leucocyte, thrombocyte counts, CRP and PCT could be calculated for day 11 to 15 (table 2). There were no significant differences between the values of fibrinogen, leucocyte, CRP and PCT between patients treated with hypothermia or for fever, but patients with fever had a higher thrombocyte count than those treated with hypothermia (p = 0.022). There were no significant differences between the values of patients with and patients without TEE.

Discussion

To our knowledge, this is the first study of a large cohort of intensive care patients who were treated with ECC and followed for the occurrence of TEE. In a small cohort group of patients (n=11) with traumatic head injury and treated with ECC, Simosa et al. found a DVT incidence of 50% [8].

In this study, we found a significantly higher risk for developing a TEE in ECC patients (37%) compared to the control group (5%). In a large register study of more than 15,000 patients with aneurismal SAH or intracerebral hemorrhage, Kshettry et al. found a general incidence of 4% for TEE. Unfortunately, they didn´t report their results with respect to the type of catheters used. [11]. In our study, there was also a significantly increased risk for TEE in ECC patients treated for fever compared to those treated with therapeutic hypothermia. This may be due to a generally higher TEE risk in patients with an infection [12], although only the thrombocyte count and no other infection parameter was higher in fever patients compared to those treated with therapeutic hypothermia. In the study population of Kshettry et al, infectious complications were a significant risk factor to suffer from TEE.

Pulmonary embolism occurred more frequently in ECC patients (12%) compared to patients who had only a CVL (3%). Kshettry reported in their study population a pulmonary embolism incidence of 1%. Several limitations of the study have to be considered: The robustness of the results is limited. For multiple logistic regression analyses, the patient number was too small. The mortality, furthermore, in the ECC group was higher than in the control group. This was probably due to the fact that the severity grade in patients of the ECC group was higher. Further studies have to distinguish if the TEE risk is also increased in patients with other diseases than SAH treated with endovascular cooling catheters.

The higher incidence of TEE in the ECC group, might have been influenced by the central venous access site. A recent Cochrane analysis showed that the incidence of thrombotic complications is as high as 22% with femoral central venous access routes, compared to subclavian catheters with only 1.9%, whereas no significant differences exist between femoral and jugular catheters [13]. In the present series, all ECCs were inserted into the femoral vein, whereas most CVLs were inserted in the subclavian vein. The risk for TEE for ECC inserted in the subclavian vein should be examined exclusively. Moreover, in a future prospective study it is recommended to perform routine screening Doppler examinations to detect asymptomatic TEE as well.

Conclusion:

Our data show that treatment with ECC increases the risk of TEE in SAH patients. Therefore, especially for fever control, non-invasive devices for surface cooling should be the first choice.

Table 1: Incidence of thrombosis, pulmonary embolism and installed Cava filters

	All patients (n=122)	Patients with central venous lines (n = 79)	Patients with endovascular cooling catheters (n = 43)		
			All (n = 43)	Treated for fever (n = 21)	Treated with hypothermia (n = 22)
Thrombosis and pulmonary embolism confirmed by sonography and/or CT scan	20 (16%)	4 (5%)	16 (37%)	11 (52%)	5 (23%)
Thrombosis confirmed by sonography	15 (12%)	4 (5%)	11 (26%)	7 (32%)	4 (19%)
Pulmonary embolism confirmed by CT scan	7 (6%)	2 (3%)	5 (12%)	4 (19%)	1 (5%)
Cava filter installed	6 (5%)	0 (0%)	6 (14%)	6 (27%)	0 (0%)

Table 2: Labor parameters analyzed. Values are given as median for day 11 – 15 after ECC onset and range

	Fibrinogen median for day 11-15 (g/l)	Leucocyte count median for day 11-15 (G/l)	Thrombocyte count median for day 11-15 (G/l)	CRP median for day 11-15 (ng/l)	PCT median for day 11-15 (ug/l)
All (n=32)	6.0 (3.6-14.6)	9.33 (2.9-19.3)	193 (85-859)	53 (2-388)	0.16 (0.01-5.57)
Fever (n=17)	6.1 (4.8-17)	9.39 (2.94-17)	253 (134-859)	65 (15-388)	0.16 (0.05-5.57)
Hypothermia (n=15)	5.6 (3.6-13)	9.28 (6.2-16.7)	152 (85-459)	44 (2.2-250)	0.16 (0.01-0.62)
Thrombosis (n=15)	5.7 (3.6-14.6)	9.44 (2.94-16.82)	253 (97-522)	65 (2.2-388)	0.15 (0.03-5.57)
No thrombosis (n=17)	6.3 (4.1-13)	9.06 (5.28-19.33)	186 (85-859)	47 (15-250)	0.19 (0.01-0.62)

Conflict of interest: Achim Müller, Andreas Lorenz, Burkhardt Seifert and Emanuela Keller declare that they have no conflict of interest.

References

1. Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. The Cochrane database of systematic reviews 2012;9:CD004128.
2. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996;347:422-5.
3. Fernandez A, Schmidt JM, Claassen J, et al. Fever after subarachnoid hemorrhage: risk factors and impact on outcome. Neurology 2007;68:1013-9.
4. Schwarz S, Hafner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. Neurology 2000;54:354-61.
5. Oh HS, Jeong HS, Seo WS. Non-infectious hyperthermia in acute brain injury patients: relationships to mortality, blood pressure, intracranial pressure and cerebral perfusion pressure. International journal of nursing practice 2012;18:295-302.
6. Broessner G, Beer R, Lackner P, et al. Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: bicenter prospective, randomized trial. Stroke 2009;40:e657-65.
7. Broessner G, Lackner P, Fischer M, et al. Influence of prophylactic, endovascularly based normothermia on inflammation in patients with severe cerebrovascular disease: a prospective, randomized trial. Stroke 2010;41:2969-72.
8. Simosa HF, Petersen DJ, Agarwal SK, Burke PA, Hirsch EF. Increased risk of deep venous thrombosis with endovascular cooling in patients with traumatic head injury. The American surgeon 2007;73:461-4.
9. Seule MA, Muroi C, Mink S, Yonekawa Y, Keller E. Therapeutic hypothermia in patients with aneurysmal subarachnoid hemorrhage, refractory intracranial hypertension, or cerebral vasospasm. Neurosurgery 2009; 64:86-92
10. Keller E, Imhof HG, Gasser S, Terzic A, Yonekawa Y. Endovascular cooling with heat exchange catheters: a new method to induce and maintain hypothermia. Intensive care medicine 2003;29:939-43.
11. Kshettry VR, Rosenbaum BP, Seicean A, Kelly ML, Schiltz NK, Weil RJ. Incidence and risk factors associated with in-hospital venous thromboembolism after aneurysmal subarachnoid hemorrhage. Journal of clinical neuroscience 2014;2:282-6
12. Tichelaar YI, Kluin-Nelemans HJ, Meijer K. Infections and inflammatory diseases as risk factors for venous thrombosis. A systematic review. Thrombosis and haemostasis 2012;107:827-37.
13. Ge X, Cavallazzi R, Li C, Pan SM, Wang YW, Wang FL. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. Cochrane database of systematic reviews 2012; 3; CD004084